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16. ABSTRACT

Mice have been exposed for durations of 6 min to 1 yr to NO_2 concentrations of 0.5 to 28 ppm. Exposed mice and control mice have then inhaled an aerosol containing a lung pathogen and the excess mortality of exposed mice (compared with control mice) has been determined. A mathematical model (similar to a previously-developed model for vegetation injury) has been been developed from an analysis of the resulting data to calculate expected excess mortality as a function of NO_2 concentration and exposure duration. Excess mortality was found to be proportional to NO_2 concentration multiplied by exposure duration raised to the 0.33 power. The concentration (c) expected to cause a certain mortality level (z), as a function of the hours of exposure (t), can be expressed as

$$c = 9.55(2.42)^{z}t^{-0.33}$$

The model has been used to calculate expected excess mortality (1.1%) if mice had inhaled the ambient NO_2 concentrations measured in downtown Chicago for each hour of 1974 (1 yr arithmetic mean of 0.05 ppm, the same as the present national ambient standard). NO_2 affects mice much more than it affects men. If men were exposed to the NO_2 dosages studied here, increased morbidity rather than increased mortality would be expected.

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An Air Quality Data Analysis System for Interrelating Effects, Standards, and Needed Source Reductions: Part 5. NO_2 Mortality in Mice

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Mice have been exposed for durations of 6 min to 1 yr to NO_2 concentrations of 0.5 to 28 ppm. Exposed mice and control mice have then inhaled an aerosol containing a lung pathogen and the excess mortality of exposed mice (compared with control mice) has been determined. A mathematical model (similar to a previously-developed model for vegetation injury) has been developed from an analysis of the resulting data to calculate expected excess mortality as a function of NO_2 concentration and exposure duration. Excess mortality was found to be proportional to NO_2 concentration multiplied by exposure duration raised to the 0.33 power. The concentration (c) expected to cause a certain mortality level (z), as a function of the hours of exposure (t), can be expressed as

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Toxicologists and pharmacologists have found that an organism's response to a drug dose is often related to the logarithm, rather than the arithmetic value, of the dose and that such response data often appear to be lognormally distributed.[1] When plotted on log-probability graph paper an approximately straight line often results. These findings suggested that plants might respond similarly to air pollutant concentrations. Leaf injury data have been analyzed for 19 plant species exposed to O_3 or SO_2 for 0.5 to 8 hr.[2] A mathematical model has been developed to express the results. A characteristic of the model is that for a given exposure duration, the percent leaf injury, as a function of pollutant concentration, tends to fit a lognormal frequency distribution. This finding for plants suggests conducting similar analyses for animals.

All three authors are with the U.S. Environmental Protection Agency Research Laboratories, Research Triangle Park, NC 27711. Dr. Larsen is an Environmental Research Engineer in the Environmental Applications Branch, Meteorology and Assessment Division, Environmental Sciences Research Laboratory. Dr. Gardner is Chief of the Biomedical Research Branch and Dr. Coffin is a Senior Science Advisor; both are in the Health Effects Research Laboratory. This is a revised version of Paper no. 77-44.3 which was presented at the 70th Annual Meeting of APCA at Toronto in June 1977.

Mice Mortality

As reported previously,[3] groups of mice have been exposed for durations of 6 min to 1 yr to NO_2 concentrations of 0.5 to 28 ppm. The mice were pathogen-free Swiss Albino females, strain CD-1 (Charles River Laboratory), weighing 20 to 25 gm. The studies of mice exposed to NO_2 concentrations greater than 0.5 ppm will be discussed first. Each mouse in these studies was exposed in an individual compartment. Control mice were treated similarly to exposed mice except that they were not exposed to NO_2.

At various times during the exposure studies, groups of 20 mice were removed from the exposure chamber, were combined with 20 control mice which had breathed only clean filtered air, and were exposed for 15 min to an aerosol of viable microorganisms (*Streptococcus pyogenes*, Group C) at a concentration of about 1 billion microbes per ml of air. Control mice were then separated from exposed mice and mortality in both groups was observed for 15 days. Replicate experiments were usually conducted. The number of mice exposed to each combination of concentration and duration is listed in Table I.

Excess mortality for the exposed mice has been calculated herein as

$$M = (E - C)(100\%)/(100\% - C) \qquad (1)$$

where

M = the % excess mortality in exposed mice
E = the % mortality in the exposed group
C = the % mortality in the control group

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Mortality in the control group usually averaged 20%. If 40% of the exposed mice were to die, this would calculate as an excess mortality of 25%. An excess mortality of 100% would be calculated if all of the exposed mice died. Eq. 1 has thus been designed to operate on a scale of 0% to 100%. This equation is known as Abbott's equation (Ref. 4, Eq. 7.2).

The data in Table I for mice exposed to 0.5 ppm are from a previous study (Ref. 5, Table 1). This previous study was quite similar to the one from which the rest of the data came.

Table I. Mortality of mice exposed to various NO_2 concentrations for various durations and then challenged with an aerosol of a lung pathogen.

NO_2 conc ppm	Exposure duration hr	Mortality Expd num	Mortality Cntl num	Population Expd num	Population Cntl num	Excess mortality %	Excess mortality z
.5	168.00	189	187	280	280	2.2	−2.02
	336.00	92	81	180	180	11.1	−1.22
	720.00	55	49	120	120	8.5	−1.38
	1440.00	78	34	100	50	31.3	−.49
	2160.00	127	72	210	180	34.1	−.41
	4320.00	84	51	120	110	44.1	−.15
	6480.00	63	52	90	90	28.9	−.55
	8760.00	26	19	30	30	63.6	.35
1.5	2.00	51	45	90	90	13.3	−1.11
	5.00	4	4	20	20	3.1	−1.86
	8.00	67	45	90	90	48.9	−.03
	18.00	9	4	20	20	31.3	−.49
	24.00	90	61	150	150	32.6	−.45
	96.00	44	31	120	120	14.6	−1.05
	126.00	11	4	20	20	43.8	−.16
	168.00	37	17	80	80	31.7	−.47
	222.00	9	4	20	20	31.3	−.49
	336.00	43	18	80	80	40.3	−.24
	504.00	35	8	60	60	51.9	.05
3.5	.50	29	19	100	100	12.3	−1.16
	1.00	53	37	200	200	9.8	−1.29
	2.00	13	8	40	40	15.6	−1.01
	3.00	75	37	200	200	23.3	−.73
	5.00	23	8	40	40	46.9	−.08
	7.00	152	56	280	280	42.9	−.18
	14.00	55	19	80	80	59.0	.23
	24.00	98	29	140	140	62.2	.31
	48.00	121	31	160	160	69.8	.52
	96.00	17	2	20	20	83.3	.97
	168.00	19	2	20	20	94.4	1.59
	384.00	15	2	20	20	72.2	.59
7.0	.50	52	27	120	120	26.9	−.62
	1.00	62	27	120	120	37.6	−.31
	1.50	61	27	120	120	36.6	−.34
	2.00	86	27	120	120	63.4	.34
14.0	.50	27	13	60	60	29.8	−.53
	1.00	36	13	60	60	48.9	−.03
	1.50	53	13	60	60	85.1	1.04
	2.00	52	13	60	60	83.0	.95
28.0	.10	60	18	100	97	50.9	.02
	.25	72	18	100	97	65.6	.40
	.42	79	18	100	97	74.2	.65
	.58	92	18	100	97	90.2	1.29

The main difference is that in the previous study the pathogen *Klebsiella pneumoniae* was used instead of *Streptococcus pyogenes*. The use of Eq. 1 should minimize any effect of using this different pathogen. A second difference is that each exposure cage had ten mice rather than one.

Log-probability Mortality Plot

The excess mortality values listed in Table I have been plotted on log-probability graph paper (Figure 1). The plot is similar to one for leaf injury (Ref. 2, Figure 2). (The method of fitting the lines to the data will be discussed later.) The ordinate is labeled both as percent excess mortality (left scale) and number of standard deviations from the median (right scale). Note that the right scale is linear. Z is a normally distributed variate with a mean of zero and a standard deviation of 1. The plotted z values are those listed in the last column of Table I.

Since air quality data are often lognormally distributed, earlier papers in this series[6] used the geometric mean and the standard geometric deviation to describe such data. The geometric mean for NO_2 air quality data at a particular site, for instance, is the concentration that is exceeded 50% of the time. Note the different use of these two parameters in Figure 1. The geometric mean (273 hr) for the mice exposed to 1.5 ppm of NO_2 is now the exposure time that yields 50% excess mortality. The standard geometric deviation (14) is the time that yields 50% excess mortality (273 hr) divided by the time that yields 16% excess mortality (19 hr).

As mentioned earlier, an organism's response to a drug dose is often related to the logarithm of the dose. In air pollution

studies, dosage is usually defined as air pollutant concentration multiplied by exposure duration (ct). For the data plotted in Figure 1, dosage (for a particular concentration) has been increased by increasing exposure duration.

For some types of effects, equal dosages (ct) may produce approximately equal effects (E), as expressed by a generalized equation:

$$E = kct \tag{2}$$

However, this will not be the case here, as will be shown in the next section (Eq. 9). Instead, the general relationship is

$$E = kct^{0.33} \tag{3}$$

Concentration will be shown to be more important than exposure duration in causing excess mortality.

The same arithmetic operations and symbols that have been used in previous papers in this series to describe air quality will be used here to describe excess mortality. The general equation (adapted from Eq. 21 in Ref. 7) for each line plotted in Figure 1 is thus

$$t = m_{gt}s_{gt}^{z} \tag{4}$$

where

t = the exposure duration in hr
m_{gt} = the gometric mean time for the particular concentration
s_{gt} = the standard geometric deviation of exposure duration
z = the number of standard deviations that the percentage mortality is located away from the median

Mortality Mathematical Model

The percent excess mortality values listed in Table I have been plotted on logarithmic graph paper (Figure 2). This plot is similar to one for leaf injury (Ref. 2, Figure 1). Since Figures 1 and 2 are similar to those for leaf injury, the same general mathematical model that was developed for leaf injury (Ref. 2, Eq. 7) can be used for excess mortality:

$$c = m_{gc\ 1\ hr}s_{gc}^{z}t^{p} \tag{5}$$

where

c = the NO_2 concentration in ppm
$m_{gc\ 1\ hr}$ = the geometric mean concentration (the concentration that kills 50% of the mice) at an exposure duration of 1 hr
s_{gc} = the standard geometric deviation (ratio of the concentration that kills 50% of the mice to the one that kills 16%)
z = the number of standard deviations from the median
t = the exposure duration in hr
p = the slope of the excess mortality isopleths on logarithmic graph paper

The z value and natural logarithms of concentration and exposure duration have been calculated for each of the separate sets of data (of 20 mice each) that comprise the pooled data listed in Table I. A standard multiple linear regression computer subroutine (weighted as specified for probit analysis, Eq. 7.7 in Ref. 4) has been used to calculate the parameters of best fit (Ref. 2, Eqs. 10–17) for Eq. 5:

$$c = 9.55(2.42)^{z}t^{-0.33} \tag{6}$$

This equation has been used to plot the expected excess mortality isopleths on Figures 2 and 3.

Concentration and time could have been switched in Eqs. 5 and 6:

$$t = m_{gt\ 1\ ppm}s_{gt}^{z}c^{p} \tag{7}$$

$$t = 933(14)^{z}c^{-3.03} \tag{8}$$

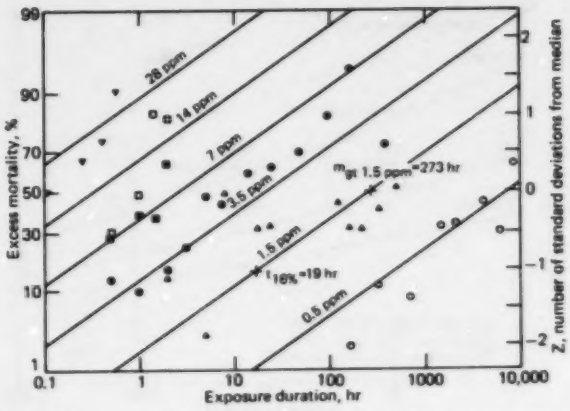

Figure 1. Excess mortality of mice exposed to various NO_2 concentrations for various durations and then challenged with an aerosol of a lung-pathogen.

Eq. 8 plots as the family of lines shown on Figure 1.

Eq. 6 and its parameters will be used here. Rearranging Eq. 6 yields

$$z = [\ln(ct^{0.33}/9.55)]/[\ln 2.42] \tag{9}$$

$$t = [9.55(2.42)^{z}/c]^{1/0.33} \tag{10}$$

Eq. 10 is mathematically equal to Eq. 8. It is necessary to use the exact constants in Eq. 6, 9, and 10 in later repetitive calculations, however, in order to keep the necessary accuracy.

The exponent of −0.33 in Eq. 6 is the slope of the excess mortality isopleths on Figures 2 and 3. This shallow slope indicates that excess mortality is changed much more by a change in concentration than it is by a change in exposure duration. For example, a concentration of 0.57 ppm for 10 hr is expected to cause an excess mortality of 1% (Figure 3). In order to increase excess mortality by a factor of 10 to 10%, time would need to be increased by a factor of 16.4, to an exposure duration of 164 hr. To accomplish this same increase in excess mortality, concentration would only need to be increased by a factor of 2.53, $16.4^{0.33}$, from 0.57 ppm to 1.44 ppm.

Analyses of Separate Data and Pooled Data

As mentioned earlier, mice were usually exposed in groups of 20 to each NO_2 concentration and duration. This can be seen for the 14 ppm exposure for instance. The population of exposed mice is 60, indicating three runs of 20 mice each. All of the mice for one run of several durations were removed from the exposure chamber at one time, combined with the controls, and exposed to the pathogen. The mice exposed for 0.5 hr were placed in the chamber 0.5 hr before the simultaneous removal,

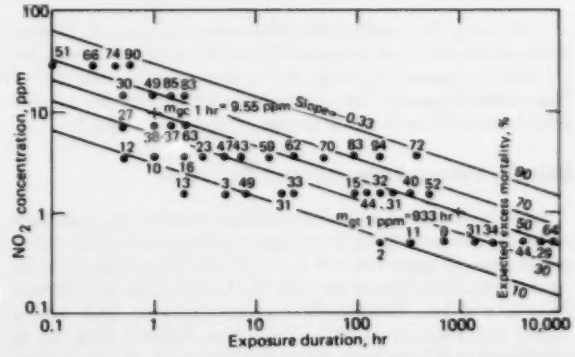

Figure 2. Percent excess mortality of mice exposed to various NO_2 concentrations for various durations and then challenged with an aerosol of a lung pathogen.

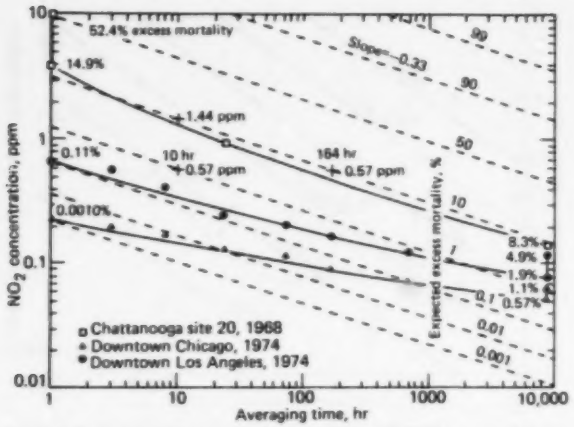

Figure 3. Excess mortality expected if mice are first exposed to the maximum NO_2 concentrations measured at sites in Chicago, Los Angeles, or Chattanooga, and then are challenged with an aerosol of a lung pathogen.

those exposed 1 hr were placed in the chamber 1 hr before the simultaneous removal, etc.

The 43 lines of data in Table I and the 43 points plotted on Figures 1 and 2 are pooled data for each concentration and exposure duration. They have been pooled to present the data more concisely. It is more appropriate statistically to treat separately each of the 156 concentration-duration data sets (together with the control mice data for each set). The three parameters in Eq. 6 are from analyses of the 156 separate data sets. As expected, the correlation between measured and modeled z values rises, from 0.72 for the separate analyses to 0.85 for the pooled analyses, since pooling reduces variability. (Only pooled data were available for the 0.5 ppm data for both types of analysis.)

As would be expected, several of the 156 sets of data involved exposures where equal numbers (7 cases) or more (4 cases) control mice than exposed mice died. In order to make these cases mathematically tractable, the number of dead NO_2 exposed mice was set to 0.5 mice greater than the number of dead control mice (e.g., last 2 columns of Table I for 1.5 ppm for 5 hr). Similarly, in one case all of the exposed mice died. For this case the number of dead exposed mice was set to 19.5 rather than 20.

Regression analyses of the pooled data produced parameters that are almost the same as did regression analyses of the separate data. The only difference is that one of the three parameters, the standard geometric deviation, rose slightly, from 2.42 for the separate data (Eq. 6) to 2.47 for the pooled data.

Mortality in Mice and Men

This paper deals only with excess mortality in mice. Deaths from pneumonia and pneumonitis have occurred in men accidentally exposed to NO_2, but at higher concentrations.[8] Exposures discussed here that caused excess mortality in mice would probably only cause excess morbidity in men.[9]

Mortality Expected from Ambient Exposures

Annual maximum air pollutant concentration as a function of air sample averaging time can be plotted on logarithmic graph paper (Figure 4 in Ref. 7). Such data (from the National Aerometric Data Bank) for year 1974 for downtown Chicago (Site 2) and Los Angeles (Site 1) and for year 1968 near a strong point source of NO_2 (Volunteer Arsenal, Site 20) in Chattanooga[10] have been plotted in Figure 3.

Volunteer Arsenal posed a unique ambient NO_2 problem, probably the worst in the U. S. It has since been controlled. The 1968 concentration data are analyzed here to show the potential problem of exposure at a site with a high peak hour to annual mean ratio. In contrast, most urban sites have the lower peak to mean ratios shown by the Chicago and Los Angeles plots.

The highest 1 hr average NO_2 concentration measured in downtown Los Angeles in 1974 was 0.64 ppm. Eq. 9 can be used to calculate the excess mortality expected if mice were exposed to this concentration for 1 hr and then challenged with an aerosol of the lung pathogen. The calculated z is -3.06. A table from a statistical text was used to determine that this corresponds to an excess mortality of 0.11%.

The arithmetic mean concentration of NO_2 in downtown Los Angeles in 1974 was 0.076 ppm. If mice had been continuously exposed to a constant concentration of 0.076 ppm for 1 yr and then were challenged with the aerosol, an excess mortality of 1.9% would have been expected. This represents about 17 times the excess mortality that would have been expected if the mice had been exposed only to the maximum hour concentration.

The reverse situation would have been expected in 1968 in Chattanooga near the strong, isolated source of NO_2 (Volunteer Arsenal). The 14.9% excess mortality expected due to the highest hour (3.80 ppm) is almost twice that expected if mice had been continuously exposed to the mean concentration (0.14 ppm) for the year.

Note that the mortality model is expected to be most accurate for the high NO_2 concentrations measured in Chattanooga, for these concentrations are closest to those to which the mice were exposed. Application of the model to the Chicago and Los Angeles data involves extrapolating to lower concentrations and may involve different mechanisms of NO_2 toxicity than those associated with acute exposure to NO_2.

The Effect of Ambient Concentration Variation

Mice have been exposed to 1.5 ppm of NO_2 intermittently,[3] for 7 hr/day, 7 days/wk, for up to 21 days. At cumulative exposures of less than 49 hr, intermittent exposure caused significantly less effect than did continuous exposure. Beyond that time, the effects of continuous and cumulative exposures were similar. This suggests that intermittent exposures to low concentrations for short periods may permit the mice to recover partially from lung injury between exposures, but that once a critical cumulative dose is attained, the recovery time is not sufficient to modify the response.

Mice have also been exposed to 3.5 ppm of NO_2 intermittently,[3] for 7 hr/day, 7 days/wk, for up to 15 days (Table II). Their excess mortality has been plotted (Figure 4) as a function of total elapsed time and cumulative exposed time. The previous continuous exposure data have also been plotted. The plots suggest that the effect of intermittent exposure is similar to the effect of continuous exposure if only the cumulative exposed time is considered. This apparent equivalency of continuous and cumulative intermittent exposures suggests that the following technique can be used to calculate expected excess mortality due to the cumulative effect of hour by hour exposure to the ambient atmosphere.

The first six hours of 1974 in downtown Los Angeles will be used as an example. The concentrations were 0.06, 0.06, 0.04, 0.04, 0.03, and 0.03 ppm. Eq. 9 can be used to calculate the z value expected after the first two hours of exposure to 0.06 ppm ($z = -5.48$). The next two hours were 0.04 ppm. Eq. 10 can be used to calculate the time that would have been necessary (6.83 hr) to achieve a z of -5.48 if the mice had been exposed to 0.04 ppm rather than 0.06 ppm. The two additional hours of 0.04 ppm (for a total of 8.83) bring z to -5.38. This is equivalent to 21.12 hr at 0.03 ppm. Two additional hours of 0.03 ppm bring t to 23.12 hr and z to -5.35. When this process is repeated (by computer) for all the hours in 1974, a z of -1.65 results. This is equivalent to a 4.9% excess mortality (Figure 3) and also to a continuous exposure for 1 yr to a

Table II. Mortality of mice exposed intermittently (7 hr/day, 7 day/wk) to an NO_2 concentration of 3.5 ppm for various durations and then challenged with an aerosol of a lung pathogen.

Exposure duration	Mortality		Population		Excess mortality	
	Expd	Cntl	Expd	Cntl		
days	num	num	num	num	%	z
1.00	47	15	80	80	49.2	−.02
2.00	36	14	60	60	47.8	−.05
3.00	40	14	60	60	56.5	.16
4.00	45	12	60	60	68.8	.49
7.00	27	5	40	40	62.9	.33
11.00	33	5	40	40	80.0	.84
15.00	32	9	40	40	74.2	.65

constant concentration of 0.111 ppm (Eq. 6), 1.46 times the actual arithmetic mean of 0.076 ppm for the year. (Any hour for which a concentration was not available was assumed to be the same concentration as that for the immediately preceding hour.)

The factor of 1.46 applies since excess mortality is more sensitive to the effect of concentration than it is to the effect of exposure duration (Eq. 3 and 9). If concentration and exposure duration were equally important (Eq. 2), the factor of 1.46 would be 1.00.

The greater the variation in hourly concentrations, the greater will be the ratio of the effective mean (0.111 ppm) to the measured mean (0.076 ppm). If all the hourly concentrations in a year were identical, the standard geometric deviation of concentration would be 1.00 and the effective ratio would be 1.00. The standard geometric deviation of 1 hr average NO_2 concentrations in downtown Los Angeles in 1974 was 1.87 (Ref. 7, Eq. 18) and the effective ratio was 1.46. In downtown Chicago in 1974 the deviation was 1.57 and the effective ratio was 1.24 (0.063 ppm/0.051 ppm).

The above calculations suggest that exposure of mice to ambient downtown Los Angeles NO_2 concentrations for the year 1974 is equivalent to a 1 yr exposure to a constant concentration of 0.111 ppm and that an excess mortality of 4.9% is expected. If the mice were exposed for 80 yr to 0.111 ppm, an excess mortality of 49% would be expected (Eq. 9). This calculation is of course a gross extrapolation from the maximum exposure duration studied (1 yr) and also suggests some unusually long-lived mice. The calculation may be helpful, however, in giving some feeling of the possible long-term effect of cumulative lung injury that can cause increased susceptibility to disease.

If mice had been exposed to ambient NO_2 concentrations at the Chattanooga site for year 1968 and had then been challenged with the pathogenic aerosol, an excess mortality of 52.4% would have been expected. This is more than three times the 14.9% mortality expected if mice had been exposed only to the maximum hour concentration of 3.80 ppm. An equivalent 52.4% excess mortality would have been expected from a 1 hr exposure to 10.07 ppm (Eq. 6). The effective ratio is thus 2.65 (10.07/3.80). This ratio is associated with the measured standard geometric deviation of 1 hr average NO_2 concentrations of 2.74 (Ref. 7, Eq. 34; 7657 hours of data available).

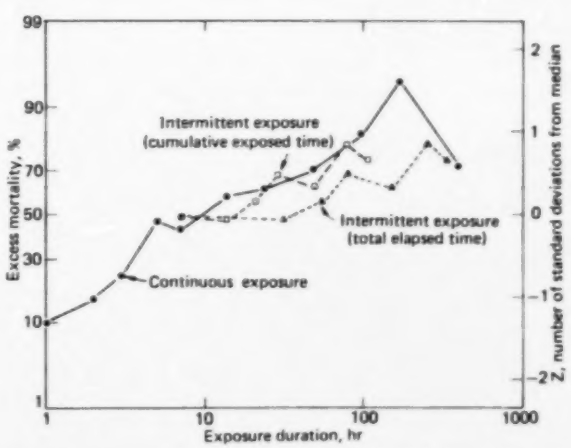

Figure 4. Excess mortality of mice exposed to 3.5 ppm of NO_2 either continuously or intermittently (7 hr/day, 7 day/wk) and then challenged with an aerosol of a lung pathogen.

Summary

Mice have been exposed for durations of 6 min to 1 yr to NO_2 concentrations of 0.5 to 28 ppm. Exposed mice and control mice have then inhaled an aerosol containing a lung pathogen for 15 min and the excess mortality of exposed mice (compared with control mice) has been determined.

A mathematical model has been developed from an analysis of the resulting data to calculate expected excess mortality as a function of NO_2 concentration and exposure duration. Excess mortality is proportional to concentration multiplied by exposure duration raised to the 0.33 power. The concentration (c) expected to cause a certain mortality level (z), as a function of the hours of exposure (t), can be expressed as

$$c = 9.55(2.42)^z t^{-0.33} \quad (6)$$

The mortality model described herein is of the same general type as a previously developed leaf injury model. The leaf injury model has been applied to 19 plant species exposed to two pollutants. Similarly, the mortality model could probably be applied to several pollutants (such as O_3 and SO_2) for a few animal species.

Acknowledgments

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